REMARKS

Claims 1-271, 273, 298, 306, and 308-338 have been cancelled. Claims 272, 274-297, 299-305, and 307 are pending. Regarding the claims, Applicants note the objection of claim 238. However, since claim 238 has been cancelled, Applicants believe that no amendment to this claim is necessary.

Applicants have also attached copies of the December 26, 1996 amendment, which lists the most recent amendments of claims 314-335 and the November 17, 1995 amendment, which lists the most recent amendment to claim 306 as requested by the Examiner in **APPENDIX C**.

Applicants also provide a copy of the initialed Information Disclosure Statement filed March 28, 2000 attached to this paper in **APPENDIX D**.

Applicants have provided a substitute specification in **APPENDIX A** along with a clean version in **APPENDIX B** as requested by the Examiner. No new matter has been added to the specification. Specifically, the specification has been amended to claim priority to the intervening Application No. 06/674,352 as suggested by the Examiner. In addition, the Brief Description of Drawings Section not entered in the amendment submitted after final rejection on March 28, 2000 has been added to the specification. Also, on page 43 of the specification, an amendment not entered in the October 13, 1992 preliminary amendment due to incorrect identification of the location has been made.

SUMMARY AND CONCLUSIONS

Applicants have addressed all of the issues remaining in the present application and therefore it is respectfully requested that the Examiner enter the above amendments and pass the application on to issue.

As indicated in the first page of this Amendment, Applicants are also filing concurrently their Request For Extension Of Time (5 Months) and authorization for the fee ($2,160.00) therefor. The Patent and Trademark Office is hereby authorized to charge the requisite $2,160.00 fee to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with this paper. In the event that any other fee(s) is/are due, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

Date: AUGUST 1, 2006

By: _____

Jeffrey T. Perez
Registration No. 52,110

Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO LIFE SCIENCES, INC.
c/o ENZO BIOCHEM, INC.
527 Madison Avenue, 9th Floor
New York, NY 10022-4304
Telephone: (212) 583-0100
Facsimile: (212) 583-0150

1812
24/
cs
2/29/96

Attorney's Docket No.: Enz-5(D5)(C2)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dean Engelhardt et al	
Serial No.:	08/486,066	Group Art Unit: 1812
Filed:	June 7, 1995	Examiner: Not Yet Known
Title:	A SUGAR MOIETY LABELED NUCLEOTIDE, AND AN OLIGO- OR POLYNUCLEOTIDE, AND OTHER COMPOSITIONS) COMPRISING SUCH SUGAR MOIETY LABELED NUCLEOTIDES(AS 2ND AM'D)	Prev. Ex'r: Qian Wang, Ph. Prev. Group Art Unit: 1812

575 Fifth Avenue (18th Floor)
New York, New York 10017
November 17, 1995

FILED BY EXPRESS MAIL

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

THIRD PRELIMINARY AMENDMENT

Dear Sirs:

This Third Preliminary Amendment follows their September 19, 1995 Supplemental Amendment to Applicants' September 12, 1995 Preliminary Amendment. Prior to the issuance of a first office action, it is respectfully requested that the following amendments also be entered in the above-identified application, which is a Rule 1.62 continuation of U.S. Patent Application Serial No. 07/960,071, filed on October 13, 1992.

AMEND THIS APPLICATION AS FOLLOWS:

In The Claims:

Add new claims 306 and 307 as follows:

306. (New) The oligo- or polynucleotide of claim 238 wherein said chemical linkage comprises or includes an olefinic bond at the ∂-position relative to P, or any of the moieties:

$$-CH=CH_2-NH-$$

$$-CH=CH-CH_2-NH-,$$

$$-CH=CH-CH_2-O-CH_2-\underset{OH}{CH}-CH_2-NH-,$$

P 30190 12/08/95 08486066 05-1135 830 103 22.00CH

$$-S-,\ -\overset{O}{\overset{\|}{C}}-O \text{ and } -O-$$

Enz-5(D5)(C2)

--307. (New) The nucleotide of claim 272 wherein said chemical linkage comprises or includes an olefinic bond at the ∂-position relative to P, or any of the moieties:

$$-CH=CH_2-NH-,$$

$$-CH=CH-CH_2-NH-,$$

$$-CH=CH-CH_2-O-CH_2-\underset{\underset{OH}{|}}{CH}-CH_2-NH-,$$

$$-S-,\ -\overset{\overset{O}{\|}}{C}-O \quad \text{and} \quad -O-$$

* * * * * * *

REMARKS

In their April 29, 1997 Amendment Under 37 C.F.R. §1.115 (page 6, fourth paragraph under REMARKS), Applicants indicated that they were awaiting receipt of a Communication Under Rule 51(4) EPC from the European Patent Office in connection with a corresponding European patent application. As the Examiner knows, the Rule 51(4) EPC Communication is the equivalent of a Notice of Allowance in the U.S. Patent and Trademark Office.

By this Supplemental Response, Applicants and their attorney are submitting correspondence and documents that were recently sent by their European associates who are handling the prosecution of their corresponding European Patent Application No. 88 10 4963.9-2105 (European Patent Publication No. 0 286 898 A2). Among these submitted papers is their European associates' April 29, 1997 letter (copy attached as Exhibit A), the Communication Under Rule 51(4) EPC dated March 12, 1997 (Exhibit B), and the claims to be granted or the allowed claims, 1-18 (Exhibit C).

Applicants respectfully request that the Examiner consider these developments in the EPO at the same time that he examines this application further. In particular, the fact that the European examiner accepted language in the independent claim where "S is a sugar moiety" should be considered when weighing Applicants' remarks in response to the objection and rejection under 35 U.S.C. §112, first paragraph.

Early and favorable action on pending claims 238-297 and 299-338 is respectfully requested.

****

SUMMARY AND CONCLUSIONS

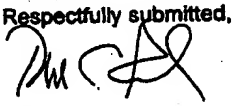
By this Supplemental Response, claims 238-297 and 299-338 are presented for further examination. No claims have been added, canceled or amended herein.

No fee is deemed necessary in connection with the filing of this Supplemental Response. If any fee is deemed necessary, however, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135.

If it would be helpful to expediting prosecution of this application, Applicants' undersigned attorney may be contacted by telephone at 212-583-0100 during normal business hours.

Early allowance of the pending claims is respectfully requested.

Respectfully submitted,



Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO DIAGNOSTICS, INC.
c/o Enzo Biochem, Inc.
527 Madison Avenue (9th Floor)
New York, New York 10022
(212) 583-0100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dean Engelhardt et. al.	)	
Serial No.	08/486,066	)	Group Art Unit: 1807
Filed:	June 7, 1995	)	Examiner: Ardin Marschel, Ph.D.
Title:	**A SUGAR MOIETY LABELED NUCLEOTIDE AND COMPOSITIONS COMPRISING SAME (as amended herein)**	)	

Enzo Diagnostics, Inc.
c/o Enzo Biochem, Inc.
527 Madison Avenue, 9th Floor
New York, New York 10022
December 26, 1996

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

AMENDMENT IN RESPONSE TO JUNE 25, 1996 OFFICE ACTION AND REQUEST FOR A THREE MONTH EXTENSION OF TIME

Sir:

This amendment is submitted in response to the June 25, 1996 Office Action issued in the above-identified application. A response to the Office Action was originally due September 25, 1996. Applicants hereby request a three month extension of time for responding to the June 25 Office Action and enclose the required fee. Accordingly, the due date for filing a response to the June 25 Office Action is now December 25, 1996. However, since December 25th was a holiday, a response to the Office Action is due the next business day -- namely, Thursday, December 26, 1996. Thus this amendment is timely filed.

Certificate of Mailing Under 37 CFR 1.8

I hereby declare that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231 on the date indicated below.

12/26/96
Date

John J. Santalone (Reg. No. 32,794)

ENZ-5 (D5)(C2)

Please amend the subject application as follows:

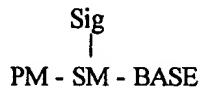
In the Title:

Delete the present title and add the following as the title: -- A SUGAR MOIETY LABELED NUCLEOTIDE AND COMPOSITIONS COMPRISING SAME --.

In the Claims:

Please add the following new claims.

-- 308 (New) A composition comprising a polymeric compound attached directly or indirectly to at least one nucleotide having the formula:



wherein PM is a phosphate moiety, SM is a ribose or a deoxyribose sugar moiety, and BASE is a pyrimidine, purine or 7-deazapurine moiety, said PM being attached to SM at the 2', 3', or 5' position of SM when said nucleotide is a ribonucleotide, and at the 3' or 5' position when said nucleotide is a deoxyribonucleotide, said BASE being attached to the 1' position of SM from the N^1 position when BASE is a pyrimidine or the N^9 position when BASE is a purine or 7-deazapurine, and said Sig is a detectable moiety covalently attached to SM directly or through a linkage group. --

-- 309. (New) The composition according to claim 308, wherein the Sig is attached to the C2' or the C3' position of SM. --

-- 310. (New) The composition according to claim 308, wherein the nucleotide comprising a deoxyribonucleotide. --

-- 311. (New) The composition according to claim 308, wherein the nucleotide comprising a ribonucleotide. --

-- 312. (New) The composition according to claim 308, wherein Sig comprise a moiety containing at least 3 carbon atoms. --

-- 313. (New) The composition according to claim 308, wherein Sig is selected from the group consisting of monosaccharides, oligosacharides and polysaccharides. --

-- 314. (New) The composition according to claim 313, wherein Sig is selected from the group consisting of triose, tetrose, pentose, hexose, heptose and octose. --

-- 315. (New) The composition according to claim 308 wherein Sig includes a glycosidic linkage moiety. --

-- 316. (New) The composition according to claim 308 wherein Sig comprises a sugar residue and said sugar residue is complexed with a binding protein therefor. --

-- 317. (New) The composition according to claim 316 wherein said binding protein comprises a lectin. --

-- 318. (New) The composition according to claim 317 wherein said lectin comprises Concanavalin A. --

-- 319. (New) The composition according to claim 308 wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a radioactive component, a metal-containing component, a fluorescent component, a chemiluminescent component, an antigen, a hapten and an antibody component. --

-- 320. (New) The composition according to claim 319 wherein said electron dense component comprises ferritin. --

-- 321. (New) The composition according to claim 317 wherein said lectin is conjugated to ferritin. --

-- 322. (New) The composition according to claim 318 wherein said Concanavalin A is conjugated to ferritin. --

-- 323. (New) The composition according to claim 319 wherein said Sig comprises a radioactive isotope. --

-- 324. (New) The composition according to claim 323 wherein said radioactive isotope comprises radioactive cobalt. --

-- 325. (New) The composition according to claim 319 wherein Sig comprises an enzyme. --

-- 326. (New) The composition according to claim 325 wherein said enzyme is selected from the group consisting of alkaline phosphatase, acid phosphatase, β-galactosidase, ribonuclease, glucose oxidase and peroxidase. --

-- 327. (New) The composition according to claim 319 wherein Sig comprises a fluorescent component. --

-- 328. (New) The composition according to claim 327 wherein said fluorescent component is selected from the group consisting of fluorescein, rhodamine and dansyl. --

-- 329. (New) The composition according to claim 308, wherein said polymeric component is selected from the group consisting of an oligo- or polynucleotide, an oligo- or polypeptide, and an oligo- or polysaccharide. --

-- 330. (New) The composition according to claim 329, wherein said polymeric component comprises an oligo- or polynucleotide. --

-- 331. (New) The composition according to claim 330, wherein said oligo- or polynucleotide comprises an oligo- or polydeoxyribonucleotide. --

-- 332. (New) The composition according to claim 330, wherein said oligo- or polynucleotide comprises an oligo- or polyribonucleotide. --

-- 333. (New) The composition according to claim 319, wherein Sig includes a hapten component capable of complexing with an antibody specific thereto. --

-- 334. (New) The composition according to claim 308, wherein Sig includes a catalytic metal-containing component. --

-- 335. (New) The composition according to claim 308, wherein said nucleotide is terminally ligated or attached to a polypeptide. --

-- 336. (New) The composition according to claim 308, wherein said Sig comprises a moiety which is detectable when said deoxyribonucleotide is incorporated with, contained in

or associated with an oligo- or polynucleotide. --

-- 337. (New) The composition according to claim 309 wherein said Sig comprises a moiety which is detectable when said ribonucleotide is incorporated with, contained in or associated with an oligo- or polynucleotide. --

-- 338. (New) The composition according to claim 308 wherein Sig is covalently attached to SM through a linkage group which comprises or includes an olefinic bond at the α-position relative to P, or any of the moieties:

$$-CH = CH_2 - NH -, \qquad -CH = CH - CH_2 - NH -,$$

$$- CH = CH - CH_2 - O - CH_2 - CH(OH) - CH_2 - NH -,$$

$$-S-, \quad -\overset{\overset{O}{\|}}{C} - O \quad \text{and} \quad - O - . \; --$$

REMARKS

Reconsideration of this application is respectfully requested. Claims 238-297 and 299-307 were pending in the subject application. Applicants have added new claims 308-338 hereinabove. Accordingly, claims 238-297 and 299-338 are now under consideration.

In the June 25, 1996 Office Action, the Examiner objected to the title of the application alleging that it is not descriptive of the elected invention. Applicants have herein deleted the previous title and have substituted the following: "A SUGAR MOIETY LABELED NUCLEOTIDE AND COMPOSITIONS COMPRISING SAME ."

In the Office Action, the Examiner also rejected claims 238, 240-272, 274-297, and 299-307 under 35 U.S.C. § 112, first paragraph, as unpatentable alleging that the disclosure is enabling only for claims limited to "covalent" attachment of the Sig moiety to the sugar (SM) via the vicinal hydroxyls at the 2' or 3' position. The Examiner argues that the only disclosed chemistry for Sig attachment to the SM moiety is via the formation of dialdehydes that are then coupled to biotin hydrazide. The Examiner maintained that another possible SM attachment of a Sig moiety at the 2', 3' or 5' hydroxyls of SM is via phosphorylation, but that this attachment is via a phosphate and is thus a PM type attachment and not an SM attachment. The Examiner maintained that any other chemistry for SM labeling with Sig is

not apparent and thus involves undue experimentation.

Applicants disagree with the Examiner's position. The Examiner indicates that if a Sig moiety were attached to the 3' or 5' hydroxyl of a particular SM moiety, it would be a PM type attachment and not an SM attachment. This is not true when the labelling is at a terminal nucleotide. In such cases the labeling may be done at the 3' or 5' hydroxyl without involvement of the phosphate group. Thus, the chemistry noted by the Examiner involving formation of dialdehydes can be used for the attachment of Sig at the 3' and 5' positions as well as at the 2' position.

Moreover, the literature at the time of the invention disclosed the transformation of sugar moieties in nucleosides and nucleotides by various techniques and at various positions. By combining the prior art techniques with the teachings of the present application, one skilled in the art could certainly practice the invention at other positions of the sugar moiety other than the 2' position. For instance, it was known that branched sugar nucleosides could be prepared by the deaminative ring-contraction -- that is, 3'-amino-3'-deoxy -glucopyranosyl derivatives of uracil and adenine could be used for the synthesis of 3'-hydroxymethyl derivatives of 3'-deoxy or 2', 3'-dideoxy uridine and adenosine.

It has also been shown that it is possible to label RNA at the 3'-terminus with fluorochrome. Thiosemicarbazides derived from tetramethylrodamine isothiocyanate (TRITC) and fluorescein isothiocyanate (FITC) were coupled to the aldehydes generated by periodate oxidation of RNAs. This technique results in breakage of the bond between the 2' and 3' positions and insertion of the label. Similarly, ferritin has been covalently attached to the sugar moiety of RNA via an avidine-biotin conjugate. The 2' and 3' hydroxyls of RNA are oxidized by periodate to dialdehydes and then coupled to one of the amino groups of 1,5-diaminopentane by Schiff base formation and subsequent $NaBH_4$ reduction. NHS-biotin is attached to the resulting RNA to form RNA-NHS-biotin conjugates. Again the labelling is at a position other than the 2' position.

Applicants also disagree with the Examiner's statement that the only disclosed chemistry for attachment of Sig to the sugar moiety is on page 53, first full paragraph. Contrary to the Examiner's statement, Example V on page 57 of the application sets forth an exemplary labeling of the phosphate moiety of oligonucleotides with biotin and polybiotinylated poly-L-lysine in the presence of carbodiimides; this chemistry could also be used for the labelling of the sugar moiety with Sig. The example references an article by Halloran and Parker, *J. Immunol.*, 96: 373 (1966), for the specifics in covalently conjugating

a protein with a polynucleotide at the PO_4 groups. As noted in the article, the OH group of the sugar residue could also be reacted with the protein carboxyl groups in the presence of carbodiimides. Accordingly, the application provides other chemistry for the labelling of the sugar moiety other than that on page 53.

The Examiner further maintains that the scope of claim 238 is broader than the available SM labeling methods because the point of attachment of Sig to SM is not limited and the attachment is not limited to a covalent character. Applicants respectfully disagree with the Examiner. As discussed above, techniques were available in the art which could be used for the attachment of groups to various positions of SM. With respect to the covalent nature of the attachments, applicants direct the Examiner to the language of claim 238 wherein it is stated that Sig is covalently attached to SM directly or through a linkage group.

Furthermore, applicants wish to point out that the disclosure of the present application has already been deemed by the U.S. Patent Office as adequate support for claims wherein Sig is attached to the sugar moiety of polynucleotides. United States Patent No. 5,260,433, which issued November 9, 1993, derived from the same parent application as that of the present application and hence has the same disclosure. In this patent, claims were allowed wherein Sig is attached to the sugar moiety: see for example, claim 1.

In sum, applicants respectfully disagrees with the Examiner's position and contend that in light of the level of knowledge in the art and the teachings set forth in the present application, a person of ordinary skill would possesses the requisite knowledge to attach the Sig moiety to SM at various positions with a reasonable expectation of success.

The Examiner also rejected claims 238-297 and 299-307 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-24 of U.S. Patent No. 5,260,433. Applicants are in the process of obtaining a Terminal Disclaimer from the assignee to alleviate this rejection.

In light of the above, applicants respectfully request withdrawal of the various rejections set forth in the June 25, 1996 Office Action and the issuance of a Notice of Allowance for the application.

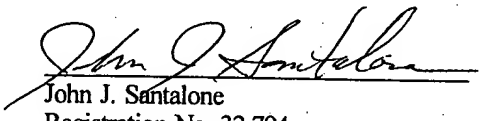
Lastly, the Examiner requested copies of the PTO forms 1449 that were submitted with applicants' September 11 and October 25, 1995 Information Disclosure Statements (IDS). The requested forms from applicants' September 11, 1995 IDS are attached hereto as

Exhibit A. Applicants are in the process of obtaining copies of the forms from their October 25, 1995 IDS and will forward them to the Examiner in the near future.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below. **(Please note that the address and telephone number for applicants' attorney has changed; a Change of Address communication is being concurrently submitted with the present response.)**

In addition to the $930 fee for the extension of time, $ 682 is due for the addition of new claims. Authorization is hereby given to charge these fees to Deposit Account No. 05-1135. If any other fee is deemed necessary, authorization is hereby given to charge the amount of such fee to Deposit Account No. 05-1135.

Respectfully,



John J. Santalone
Registration No. 32,794
Attorney for Applicants

Enzo Diagnostics, Inc.
c/o Enzo Biochem, Inc.
527 Madison Avenue, 9th Floor
New York, New York 10022
(212) 583-0100

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-5(D5)(C2)	Serial No. 08/486,068
	Applicants: Dean L. Engelhardt et al.	
	Filed: June 7, 1995	Group: 1631

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO-PRIATE
AM		4 2 6 0 7 3 7	4/7/81	Scherberg	536	28	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES	TRANSLATION NO
		~~2 0 1 0 4 0 8A~~		~~GB~~				
AM		2 9 1 5 0 8 2A 1		DE				
AM		2 9 1 5 0 8 2C 2		DE				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AM		Kochetkov, N.K. and Budovskii, E.I., Editors, Organic Chemistry of Nucleic Acids, Part B, Chapter 9, Pages 449-476, Planum Press, London and New York (1972)
		Armgstrong, V.W. and Eckstein, R., Eur. J. Biochem 70:33-38 (1976)
		Rozovskaya T.A. et al., Molekulyarnaya Biologiya 11(3):598-610 (1977)
		Petrov, A.I. and Sikhourukov B.I., Nucleic Acids Research 8(18):4221-4234 (1980)
		Petrov,,A.I., Nucleic Acids Research 8(223):5931-5929 (1980)
		Hiratsuka T., and Uchida, K., Biochemica et Biophysica Acta 320:365-647 (1973)
		Bauman, J.G.J. et al., J. Histochem. Cytochem. 29:227-237 (1981)
		Broker, T.R. et al., Nucleic Acid Research 5(2):363-384 (1978)

EXAMINER A. H. Marschel DATE CONSIDERED 4-14-00

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-5(D5)(C2)	Serial No. 08/466,066
	Applicants: Dean L. Engelhardt et al.	
	Filed: June 7, 1995	Group: 1634/631

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO-PRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANS-LATION YES	TRANS-LATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AM		Sodja, A. and Davidson, N., Nucleic Acid Research 5(2):385-401 (1978)
		Daniel, F.B. and Beerman, E.J. Biochemistry 15:565-568 (1976)
		Eberhard W. et al., Nucleic Acids Research Symposium Series Exhibit 9:15-19 (1981)
		Saffhill, R., and Hall, J.J., Carbohydrates Nucleosides Nucleotides 8:573-583 (1981)
		Erlanger, B.F. et al., Proc. Natl. Acad. Sci. 52:68-74 (1964)
		Suzuld S. et al., Bioinorganic Chemistry 3:281-293 (1974)
		Manning, J. et al., Biochemistry 16(7):1364-1370 (1977)
V		Avrameas S., Immunochemistry, Vol. 6:43-52 (1969)

EXAMINER Andrew Marschel DATE CONSIDERED 4/14/00

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.